DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

FDA PUBLIC HEALTH ADVISORY

Subject: **REPORTS OF DIABETES AND HYPERGLYCEMIA IN PATIENTS RECEIVING PROTEASE INHIBITORS FOR THE TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV)**

Dear Health Care Professional:

The Food and Drug Administration would like to call to your attention recent post marketing reports of new onset diabetes mellitus, hyperglycemia or exacerbation of existing diabetes mellitus occurring in HIV-infected patients receiving protease inhibitor therapy. At the present time there exists no conclusive evidence establishing a definite causal relationship between protease inhibitor therapy and the incidence of diabetes and hyperglycemia. Based on present reporting, we believe the occurrence of this event is relatively infrequent. As such, patients for whom these products are indicated should not discontinue therapy without consulting their health care professional. However, given the potential seriousness of this complication, we believe that patients and health care professionals should be notified of this information.

SUMMARY OF REPORTS

- As of May 12, 1997, there have been 83 cases reported to FDA of diabetes mellitus or hyperglycemia in HIV-infected patients who were receiving anti-retroviral protease inhibitor therapy; 27of the 83 cases were reported to require hospitalization. Fourteen patients were known to be diabetic at baseline; for these patients, there was a loss of glucose control. The average time of onset was approximately 76 days after initiating protease inhibitor therapy, but occurred as early as four days after starting therapy. Five cases of diabetic ketoacidosis occurred, including patients who were not reported to be diabetic at baseline; however, the baseline status of these patients is not well characterized.

- Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for the treatment of these events. On an average, fifty percent of patients discontinued their protease inhibitor therapy as a result of this acute adverse event. Hyperglycemia persisted in some patients after protease inhibitor therapy was withdrawn including patients not known to be diabetic at baseline; however a causal relationship between protease inhibitor therapy and these events has not been established.

- Many of these reports occurred in patients with confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.

- Diabetes and hyperglycemia have been reported to varying degrees for Crixivan® (indinavir), Invirase ® (saquinavir), Norvir® (ritonavir) and Viracept® (nelfinavir).

FDA will continue close monitoring for additional events. We encourage all health care professionals to report any cases of diabetes or hyperglycemia, or any other serious toxicity associated with the use of protease inhibitors, to the FDA's MEDWATCH program at 1-800-FDA-1088/fax 1-800-FDA-0178; or to the respective pharmaceutical manufacturers:

Crixivan® (indinavir), Merck Research Laboratories, 1-800-672-6372
Invirase® (saquinavir), Hoffman-La Roche, 1-800-526-6367
Norvir® (ritonavir), Abbott Laboratories, 1-800-633-9110
Viracept® (nelfinavir), Agouron Pharmaceuticals, 1-888-847-2237

Sincerely yours,

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research